PTA-2104. A Chinese Hamster Ovary (CHO) cell line expressing CTLA4Ig (CTLA4Ig-24) was deposited with ATCC on May 31, 1991, and has been accorded ATCC accession number CRL-10762.

Applicants maintain that during the pendency of the subject application, access to the ATCC deposits make by the Applicants will be afforded to one determined by the Commissioner to be entitled thereto under 35 U.S.C. §1.14 and §122. Additionally, all restrictions on the availability to the public of the material deposited under ATCC Accession Nos. 69627, 68628, 68629, PTA-2104 and CRL-10762 will be irrevocably removed upon the issuance of a patent from the subject application. Furthermore, the above deposits will be maintained by the ATCC for a period of 30 years from the date of deposit or at least 5 years after the last request for a sample of the deposited material, whichever is longer. Where the ATCC cannot furnish samples of the above deposits for any reason, Applicants shall make a replacement deposit, of the material which was originally deposited, within three months of receiving notification that the ATCC cannot furnish samples.

REMARKS

Claims 1-18 are being examined.

The Patent Office has indicated in the January 23, 2003 Office Action that only claims 1-9 and 11-18 are now pending in the in the subject application. However, Applicants respectfully point out that the October 3, 2002 Office Action at page 1, first full paragraph, indicated that Group I encompasses claims 1-18. On October 15, 2002, applicants elected, with traverse, the invention of Group I in response to the Office Action dated October 3, 2002. Accordingly, claims 1-18 of Group I are now being examined. In the January 23, 2003 Office Action, at paragraph 2, the Office took the position that claim 10 has been withdrawn and deemed part of a non-elected invention. No explanation is given.

Amendments to claims 6, 23 and 31 merely deletes a reference to ATCC deposit HB-11944 because the claims are directed to the use of anti-CD28 monoclonal antibodies and hybridoma deposit HB-11944 does not produce such an antibody.

The amendments to the specification on pages 9 and 12 merely change references for nucleic acid sequences (SEQ ID NO:6) to recite their corresponding amino acid sequences (SEQ ID NO:7). Support for these changes can be found in originally filed Figure 5.

The Patent Office has requested amendment of the specification to recite the date of deposit and the complete name and address of the depository.

Amendment to page 15 and 16 comply with the Office's request for the complete name and address of the ATCC depository. Amendments to the specification on page 15 and 16 add the proper name and address of the ATCC depository.

Additionally, an amendment to the specification on page 15 deletes a reference to ATCC deposit HB-11944 because page 15 describes the use of anti-CD28 monoclonal antibodies and hybridoma deposit HB-11944 does not produce such an antibody

Amendments to page 30 comply with the Office's request regarding deposit dates for deposits made by Applicants including: B7Ig, CD28Ig, L104EA29YIg, CTLA4Ig and CTLA4Ig-24.

However, Applicants wish to point out that the following ATCC deposits were not made by the Applicants but are commercially available from ATCC:

1. ATCC HB-253,
2. ATCC CRL-2223,
3. ATCC CRL-2226,

4. ATCC HB-301,
5. ATCC HB-304,
6. ATCC HB 11341,
7. ATCC HB-10916,
8. ATCC HB-12055,
9. ATCC HB-12056,
10. ATCC HB-9110,
11. ATCC HB-9579,
12. ATCC TIB-213,
13. ATCC CRL-1878,
14. ATCC HB-233,
15. ATCC CRL-2252,
16. ATCC TIB-237,
17. ATCC HB-202,
18. ATCC HB-244,
19. ATCC TIB-217,
20. ATCC HB-203,
21. ATCC HB-226 and
22. ATCC TIB-218.

These biological deposits are described in the subject application and are commercially available from the ATCC depository.

37 CFR 1.802 recites that "Biological material need not be deposited, inter alia, if it is known and readily available to the public..." MPEP 2404.01 recites that the "Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material."

Applicants attach copies of catalogue information for these deposits accessible from the ATCC web-site www.ATCC.org, which demonstrates the commercial availability of these deposits (EXHIBIT 1). Therefore, disclosure of the catalogue number (i.e. ATCC number) and name of the company or organization material (i.e. ATCC) from which to obtain the biological material and its location (i.e. 10801 University Blvd., Manasas, VA 20110-2209) as shown in the subject application is sufficient disclosure to meet 35 USC 112 requirements.

The amendments to the specification on page 30 merely adds the address for ATCC, the date of ATCC deposit and that the ATCC deposits for B7Ig, CD28Ig, L104EA29YIg and CRL-10762 were deposited pursuant to the Budapest Treaty. Support for these changes can be found at page 2, lines 23-25, page 7, line 31 to page 8, line 6 and page 15, lines 21-29.

Accordingly, the changes do not involve new matter and entry of the changes is respectfully requested.

SPECIES RESTRICTIONS

The Patent Office is requiring a species election of the diseases listed in claim 30 of Group I, however, claim 30 does not recite any diseases. The Applicants assume that the Patent Office meant claim 13 and will respond accordingly.

In response, Applicants hereby elect, with traverse, the species of immune disorders associated with transplant rejection. As with any species election, applicants understand that the claims will be restricted to the species only if no generic claim is found allowable.

Applicant respectfully requests that the Examiner reconsiders and withdraws the species election requirement.

No fee, other than the filing fee, is deemed necessary in connection with the filing of this Amendment. If any additional fee is necessary, the Patent Office is authorized to charge the additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

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MARKED UP VERSION OF THE AMENDMENTS TO THE SPECIFICATION

Please amend the subject application as follows.

In the Claims

Please amend the following claims

-- 6. (amended) The method of claim 5, wherein the soluble CTLA4 molecule is CTLA4Ig (ATCC 68629) or L104EA29YIg (ATCC PTA-2104); wherein the soluble CD28 molecule is CD28Ig (ATCC 68628); wherein the soluble B7 molecule is B7Ig (ATCC 68627); wherein the anti-B7 monoclonal antibody is ATCC HB-253, ATCC CRL-2223, ATCC CRL-2226, ATCC HB-301 or ATCC HB-11341; wherein the anti-CTLA4 monclonal antibody is ATCC HB-304; and wherein the anti-CD28 monoclonal antibody is [ATCC HB 11944 or]mAb 9.3.--

-- 23. (amended) The pharmaceutical composition of claim 22, wherein the soluble CTLA4 molecule is CTLA4Ig (ATCC 68629) or L104EA29YIg (ATCC PTA-2104); wherein the soluble CD28 molecule is CD28Ig (ATCC 68628); wherein the soluble B7 molecule is B7Ig (ATCC 68627); wherein the anti-B7 monoclonal antibody is ATCC HB-253, ATCC CRL-2223, ATCC CRL-2226, ATCC HB-301 or ATCC HB-11341; wherein the anti-CTLA4 monclonal antibody is ATCC HB-304; and wherein the anti-CD28 monoclonal antibody is [ATCC HB 11944 or]mAb 9.3.--

--31. (amended) The kit of claim 30, wherein the soluble CTLA4 molecule is CTLA4Ig (ATCC 68629) or L104EA29YIg (ATCC PTA-2104); wherein the soluble CD28 molecule is CD28Ig (ATCC 68628); wherein the soluble B7 molecule is B7Ig (ATCC 68627); wherein the anti-B7 monoclonal antibody is ATCC HB-253, ATCC CRL-2223, ATCC CRL-2226,

ATCC HB-301 or ATCC HB-11341; wherein the anti-CTLA4 monclonal antibody is ATCC HB-304; and wherein the anti-CD28 monoclonal antibody is [ATCC HB 11944 or]mAb 9.3.--

In the Specification

Please replace the paragraph on page 9 beginning at line 23 and ending at line 29 with the following:

-- "CTLA4Ig" is a soluble fusion protein comprising an extracellular domain of wild type CTLA4, or a portion thereof that binds a B7, joined to an Ig tail. A particular embodiment comprises the extracellular domain of wild type CTLA4 starting at methionine at position +1 and ending at aspartic acid at position +124; or starting at alanine at position -1 to aspartic acid at position +124; a junction amino acid residue glutamine at position +125; and an immunoglobulin portion encompassing glutamic acid at position +126 through lysine at position +357 (Figure 5 and SEQ ID NO: [6]7). --

Please replace the paragraph on page 12 beginning at line 2 and ending at line 7 with the following:

-- As used herein "the extracellular domain of CTLA4" is any portion of CTLA4 that recognizes and binds a B7. For example, an extracellular domain of CTLA4 comprises methionine at position +1 to aspartic acid at position +124 (Figure 5 and SEQ ID NO: [6]7). Alternatively, an extracellular domain of CTLA4 comprises alanine at position –1 to aspartic acid at position +124 (Figure 5 and SEQ ID NO: [6]7). The extracellular domain includes fragments or derivatives of CTLA4 that bind a B7. --

Please replace the paragraph on page 15 beginning at line 15 and ending at line 29 with the following:

-- The first agent preferably acts by interfering with the interaction between a receptor on a lymphocyte (e.g., CD28 and/or CTLA4) and its ligand (e.g., B7-1 and/or B7-2). Examples of the first agent include, but are not limited to, molecules such as an antibody (or portion or derivative thereof) that recognizes and binds to the receptor or the ligand; a soluble form (or portion or derivative thereof) of the receptor or the ligand such as soluble CTLA4; a peptide fragment or other small molecule designed to interfere with the lymphocytic signal through the receptor/ligand mediated interaction. In a preferred embodiment, the first agent is a soluble CTLA4 molecule, such as CTLA4Ig (ATCC 68629) or L104EA29YIg (ATCC PTA2104), a soluble CD28 molecule such as CD28Ig (ATCC 68628), a soluble B7 molecule such as B7Ig (ATCC 68627), an anti-B7 monoclonal antibody (e.g. ATCC HB-253, ATCC CRL-2223, ATCC CRL-2226, ATCC HB-301, ATCC HB-11341 and monoclonal antibodies as described in references 80-81), an anti-CTLA4 monclonal antibody (e.g. ATCC HB-304, and monoclonal antibodies as described in references 82-83) and/or an anti-CD28 monoclonal antibody (e.g. [ATCC HB 11944 and]mAb 9.3 as described in reference 79). American Type Culture Collection (ATCC) is located at 10801 University Blvd., Manasas, VA 20110-2209. --

Please replace the paragraphs on page 16 beginning at line 1 and ending at line 27 with the following:

-- The second agent acts by interfering with the interaction between a second receptor on a lymphocyte (e.g., CD154) and its ligand (e.g., CD40). Examples of the second agent include, but are not limited to, molecules such as an antibody (or portion or derivative thereof) that recognize and bind the second receptor or the ligand such as an anti-CD154 monoclonal antibody; a soluble form (or portion or derivative thereof) of the receptor or the ligand; a

peptide fragment or other small molecule designed to interfere with the lymphocytic signal through the second receptor/ligand mediated interaction. In a preferred embodiment, the second agent is an anti-CD154 (e.g. MR1 as described in reference 56, ATCC HB-10916, ATCC HB-12055 and ATCC HB-12056) and/or anti-CD40 monoclonal antibody (e.g. ATCC HB-9110). American Type Culture Collection (ATCC) is located at 10801 University Blvd., Manasas, VA 20110-2209.

The third agent interferes with adhesion molecule (e.g. LFA-1) interactions with its ligands. Examples of adhesion molecules and ligands include, but are not limited to, LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18), p150,95 (CD11c/CD18), ICAM (1, 2 and 3), VLA-1, CD44, CD62 (E, L and P), CD106, fibrinogen, α–actinin, filamin and cytohesin-1. LFA-1 ligands such as ICAM-1, ICAM-2, ICAM-3, α-actinin, filamin and cytohesin-1, etc., can be located on another cell or in the extracellular matrix. Examples of the third agent include, but are not limited to: molecules such as an antibody (or portion or derivative thereof) that recognizes and binds adhesion molecules or its ligands; a soluble form (or portion or derivative thereof) of the adhesion molecule or its ligand; a peptide fragment or other small molecule designed to interfere with the adhesion molecule/ligand interaction. In a preferred embodiment, the third agent is an anti-LFA-1 (e.g. ATCC HB-9579, and ATCC TIB-213), anti-ICAM-1 (e.g. ATCC CRL-1878 and ATCC HB-233), anti-ICAM-2, anti-ICAM-3, anti-α-actinin (e.g. ATCC CRL-2252), anti-filamin, anti-cytohesin-1, anti-CD11a (e.g. M17/5.2 ATCC TIB-237, ATCC HB-202, ATCC HB-244, and ATCC TIB-217) and/or anti-CD18 (ATCC HB-203, ATCC HB-226 and ATCC TIB-218) monoclonal antibody. American Type Culture Collection (ATCC) is located at 10801 University Blvd., Manasas, VA 20110-2209.

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Please replace the paragraph on page 30 beginning at line 4 and ending at line 6 with the following:

-- DNA encoding the amino acid sequences corresponding to B7Ig, CD28Ig and CTLA4Ig has been deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manasas, VA 20110-2209, under the Budapest Treaty on May 31, 1991, and has been accorded ATCC accession numbers 68627, 68628 and 68629, respectively. DNA encoding the amino acid sequence corresponding to L104EA29YIg has been deposited with the ATCC under the Budapest Treaty on June 19, 2000, and has been accorded ATCC accession number PTA-2104. A Chinese Hamster Ovary (CHO) cell line expressing CTLA4Ig (CTLA4Ig-24) was deposited with ATCC on May 31, 1991, and has been accorded ATCC accession number CRL-10762.

Applicants maintain that during the pendency of the subject application, access to the ATCC deposits make by the Applicants will be afforded to one determined by the Commissioner to be entitled thereto under 35 U.S.C. §1.14 and §122. Additionally, all restrictions on the availability to the public of the material deposited under ATCC Accession Nos. 69627, 68628, 68629, PTA-2104 and CRL-10762 will be irrevocably removed upon the issuance of a patent from the subject application. Furthermore, the above deposits will be maintained by the ATCC for a period of 30 years from the date of deposit or at least 5 years after the last request for a sample of the deposited material, whichever is longer. Where the ATCC cannot furnish samples of the above deposits for any reason, Applicants shall make a replacement deposit, of the material which was originally deposited, within three months of receiving notification that the ATCC cannot furnish samples. --